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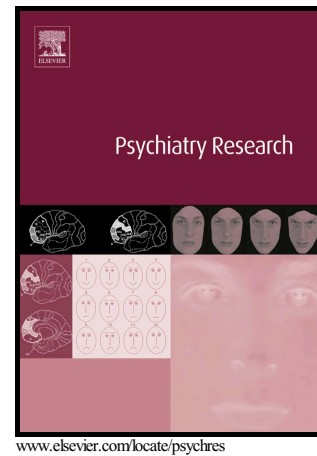
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Physical activity as a vital sign in patients with bipolar disorder

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Abstract

The most significant contributor to premature mortality in patients with bipolar disorder is preventable cardiovascular diseases. This study investigated if the Physical Activity Vital Sign (PAVS) assessment (two questions which clarify if a person meets the recommended 150 minutes of physical activity per week) can identify patients with bipolar disorder at higher risk of cardio-metabolic abnormalities. Clinical differences between those who adhere and those who did not adhere to the physical activity guidelines were investigated using an ANCOVA controlling for age and gender. Sixty-five (29♂) in- and outpatients with bipolar disorder (age=45.1±9.8years) completed the PAVS-questions, underwent full-fasting metabolic screening, and performed a six-minute walk test (6MWT). Those patients not meeting the physical activity recommendations had a higher body mass index, performed worse on

the 6MWT and were at a significantly higher risk for cardio-metabolic diseases. Relative risks ranged from 1.33 for having dyslipidemia to 5.33 for hyperglycemia. The current data offer the first evidence that the PAVS assessment might be a useful vital sign in the routine assessment of in- and outpatients with bipolar disorder.

Keywords: physical activity; exercise; obesity; hypertension; metabolic syndrome; bipolar disorder

1. Introduction

Patients with bipolar disorder have higher levels of morbidity and mortality than the general population (De Hert et al., 2011). A recent meta-analysis (Walker et al., 2015) demonstrated that mortality rates are approximately two to three times higher than those of the general population. The underlying causes for the increased premature mortality are complex and multi-factorial (Hayes et al., 2015), but increased comorbid cardio-metabolic disease (Goldstein et al., 2015) is one of the most important risk factors. For example, compared with age- and gender matched general population groups, bipolar patients have a double increased risk for metabolic syndrome (odds ratio=1.98; 95% CI=1.74-2.25) (Vancampfort et al., 2013c) and diabetes (relative risk=1.98; 95% CI, 1.6-2.4) (Vancampfort et al., 2015b). Next to genetic predisposition (Ellingrod et al., 2012), shared pathophysiological mechanisms (Dargél et al., 2015), and side-effects of psychotropic medication (Vancampfort et al., 2015c), poor lifestyle habits including higher prevalence of smoking (Jackson et al., 2015) and substance abuse (Hjorthøj et al., 2015) and lower levels of physical activity (Janney et al., 2014) play prominent roles in the cardio-metabolic risk profile of people with bipolar disorder.

In addition to smoking cessation interventions (Mitchell et al., 2014), there is growing recognition of the importance of encouraging patients with bipolar disorder to sit less and move more as an essential, achievable strategy to improving health outcomes in this group (Vancampfort et al., 2015e). Although the evidence base for the mental health benefits of physical activity for patients with bipolar disorder is relatively limited in comparison to other mental disorders (Thomson et al., 2015),

there is overwhelming evidence for the benefits of physical activity for improving physical health outcomes in the general population, with an established relationship between time spent being physically active, morbidity and mortality (Kodama et al., 2009). Nonetheless, despite progress in achieving mainstream recognition of the therapeutic benefits of integrating physical activity interventions as a routine component of treatment, physical activity remains an underutilized component of standard care (Vancampfort et al., 2015d). A comprehensive treatment plan for bipolar disorder should therefore consider physical activity as an essential medicine to decrease the risk of cardiovascular disease and address the premature mortality gap (Vancampfort et al., 2015d). An essential first step to promoting physical activity among bipolar disorder patients, is to ensure the routine assessment of physical activity, including time spent participating in structured exercise and incidental physical activity (Sallis, 2011). Without an understanding of current physical activity levels, it is difficult to advise patients on how to optimize their physical activity habits. The International Organization of Physical Therapists in Mental Health Guidelines for people with severe mental illness (Vancampfort et al., 2012) recommends that patients should achieve at least 150 min per week of moderate intensity (e.g., brisk walking) physical activity, or 75 min per week of vigorous physical activity (e.g., jogging). A major challenge to physical activity promotion in mental health care settings is time, specifically the competing demands in a typical 15–20 min office visit (De Hert et al., 2011). To date, there are currently no physical activity tools that quickly assess compliance with the international physical activity recommendations. Currently used questionnaires in clinical practice such as Baecke Physical Activity Questionnaire (Baecke et al., 1982) do not capture the time spent physically active at all while others such as the International Physical Activity Questionnaire (Craig et al., 2003) are intended for epidemiological research while its validity in clinical settings has been questioned (Rosenbaum and Ward, 2016; Vancampfort et al., 2016b).

Given that physical activity participation has been shown to be a better predictor of morbidity in comparison to other traditional 'vital signs' such as blood pressure, the concept of incorporating physical activity as a vital sign for every patient has gained increasing clinical attention (Sallis, 2011). The physical activity vital sign (PAVS) is a two-question measure to assess the adherence to the international recommendation of 150 minutes per week of moderate to vigorous physical activity. To our knowledge, no study has considered whether using the PAVS-assessment can identify patients with bipolar disorder at greatest risk of cardio-metabolic disease (Greenwood et al., 2010). Given the

mentioned, the aim of the current study was to investigate if there are differences in cardio-metabolic risk factors (body mass index (BMI) overweight, abdominal obesity, hypertension, dyslipidemia, hyperglycemia and metabolic syndrome (MetS)) and functional exercise capacity among patients that do and do not meet the recommendations of 150 minutes per week of physical activity assessed by the PAVS-method. We hypothesized that patients with bipolar disorder failing to achieve the physical activity recommendations according to the PAVS-method had a worse functional exercise capacity and a higher risk for cardio-metabolic diseases.

2. Methods

2.1. Participants and procedure

Over a 9-month period, in- and outpatients with a DSM 5 diagnosis of bipolar disorder (American Psychiatric Association, 2013) at the University Psychiatric Center KU Leuven were invited by their treating psychiatrist to participate. All participants in the current study received care as usual including psychomotor therapy (relaxation, body awareness exercises and at least 3 times per week during 45 to 60 minutes physical activity). In the evenings all participants had free access to sports facilities (e.g., badminton, soccer, netball, although we did not systematically assess the attendance. Only patients who were able to concentrate in order to complete the questionnaires, following an initial assessment by the treating psychiatrist, were included. Participants were excluded if they had a current co-morbid DSM 5 diagnosis of substance use disorder (due to the potential impact on functional exercise testing) or if they met the absolute somatic contra-indications for exercise testing according to the American College of Sports Medicine (2009) (including evidence of significant cardiovascular, neuromuscular and endocrine disorders). All patients received a general physical examination and baseline electrocardiogram before testing. Participants were asked the PAVS-questions, underwent a full-fasting metabolic screening, and performed a six-minute walk test (6MWT) (ATS, 2002) to determine the functional exercise capacity. The study procedure was approved by the Ethical and Scientific Committee of the University Psychiatric Center KU Leuven, campus Kortenberg, Belgium. All participants gave their written informed consent.

2.2. Demographical data

Demographic data were obtained from medical records. In addition, smoking status and number of cigarettes smoked per day were recorded.

2.3. Physical activity vital sign (Greenwood et al., 2010)

Physical activity was assessed using the PAVS, comprising of two simple questions (Greenwood et al., 2010). The first question is, "On average how many days per week do you engage in moderate to vigorous physical activity like a brisk walk?" The second question is: "On those days, how many minutes do you engage on average in physical activity at this level?" Next the clinician multiplied the two responses together to calculate the minutes per week of self-reported moderate to vigorous physical activity and verified whether the patient was achieving the internationally endorsed recommended target of 150 minutes per week of moderate to vigorous physical activity or not (yes=1; no=0) (Coleman et al., 2012; Sallis et al., 2015; Vancampfort et al., 2012).

2.4. Functional exercise capacity - 6-minute walk test

The 6-minute walk test (6MWT) was performed according to the American Thoracic Society (ATS, 2002) guidelines in an indoor corridor with limited external stimuli. The total distance walked in 6 minutes was recorded to the nearest decimetre. The 6MWT is a reliable and valid method to assess functional exercise capacity in people with bipolar disorder (Vancampfort et al., 2015a; Vancampfort et al., 2016a).

2.5. Metabolic and anthropometric measurements

Body weight was measured in light clothing to the nearest 0.1kg using a SECA beam balance scale, and height to the nearest 0.1cm using a wall-mounted stadiometer. Waist circumference (WC) was measured to nearest 1cm at the level of the umbilicus and at the end of expiration with the participant

upright and his/her hands by the side. Blood pressure was recorded twice in the sitting position after a five minutes rest with an Omron M6 (HEM-7001-E) (Omron® Healthcare Europe). The average of both measures was taken. Patients received a full fasting laboratory screening. The presence of abdominal obesity, hypertension, dyslipidemia (hypertriglyceridemia and/or hypoalipoproproteinemia), hyperglycemia and metabolic syndrome (MetS) was assessed using the International Diabetes Federation (IDF) criteria (Alberti et al., 2005).

2.6. Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)

The QIDS-SR (Rush et al., 1996) consists of 16 items that assess the severity of depressive symptomatology in the past week on a 0 to 3-scale. The total score ranges from 0 to 27.

2.7. Medication use

Current antipsychotic medication use was recorded for each patient and the daily dosage of each antipsychotic was converted into a daily equivalent dosage of chlorpromazine (Gardner et al., 2010). If patients were treated with a combination of antipsychotics, all obtained equivalent dosages of chlorpromazine were summed together. Next to antipsychotic medication use, we also assessed the daily dosage of mood stabilizers if present in at least 10 participants.

2.8. Statistical analyses

Differences in age between those who adhere and those who did not adhere to the physical activity guidelines were assessed with a t-test while differences in gender distribution were investigated with Fisher's Exact test. As in people with bipolar disorder older age (Vancampfort et al., 2013a) and female gender (Janney et al., 2014) might be related to lower physical activity levels, clinical differences between those who adhere and those who did not adhere to the physical activity guidelines were investigated using an ANCOVA controlling for age and gender. Relative risks when not adhering to the recommendations were calculated. A priori, a level of significance was set at

$P < 0.05$. Statistical analyses were performed using the statistical package SPSS version 22.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Participants

Out of 85 patients with bipolar disorder, 73 (86%) met the inclusion criteria of which 8 declined to participate. Reasons for exclusion are presented in Figure 1. The gender distribution of the final included sample was 29 men (44.6%) (45.1 ± 9.8 years; $BMI = 26.7 \pm 3.0$) and 36 women (55.4%) (43.8 ± 11.6 years; $BMI = 25.8 \pm 5.2$). Across the entire sample, age ranged from 19 to 64 years. There were 19 outpatients (47.8 ± 7.9 years; $BMI = 26.3 \pm 5.2$) and 46 inpatients (42.9 ± 11.6 years; $BMI = 26.1 \pm 4.0$). All individuals were Caucasians. The mean chlorpromazine equivalent dose was 419.7 ± 269.8 mg/day ($N = 51$), the mean lithium dose 828.3 ± 476.2 mg/day ($N = 23$) and the mean valproic acid dose 1614.3 ± 574.9 mg/day ($N = 14$).

Forty-six patients (71%) adhered to the physical activity recommendations as formulated by the PAVS-assessment method (397.6 ± 205.3 min versus 128.7 ± 85.1 min, $P < 0.001$).

3.2. Differences between those who adhered and did not adhere to the recommendations

Those who do not adhere to the physical activity recommendations tended ($P = 0.08$) to be older (48.0 ± 10.4 versus 42.7 ± 10.7 years), were more likely to be women (12/36 versus 7/29, $P = 0.16$), had a longer duration of illness (21.5 ± 11.8 versus 13.9 ± 9.5 years, $P = 0.008$), and had a higher QIDS score (12.9 ± 5.7 versus 5.6 ± 4.1 , $P < 0.001$). There were no significant differences in psychotropic medication doses between those who adhere and not adhere to the physical activity recommendations. An overview of the clinical differences between those who adhere and not adhere to the physical activity recommendations controlled for age and gender is presented in Table 1. Those who did not adhere to the minimum physical activity recommendations as formulated by the PAVS-method had a higher BMI, performed worse on the 6MWT, and had a higher risk for abdominal obesity, hypertension, hyperglycemia and MetS. The relative risks ranged from 1.33 (0.80-2.21) for having

dyslipidemia to 3.39 (1.84-6.24) for metabolic syndrome and 5.33 (2.14-13.27) for hyperglycemia (see Table 2).

4. Discussion

4.1. General findings

The current study demonstrates that patients with bipolar disorder who fail to achieve the physical activity recommendations, according to the PAVS-method, have an impaired functional exercise capacity and are at a significantly higher risk for cardio-metabolic diseases. Specifically, patients with bipolar disorder not meeting the recommended amount of physical activity are at a three and five times increased risk of hyperglycaemia and MetS. The current data underscore the importance of motivating patients with bipolar disorder to adhere to the general physical activity recommendations. Secondly, our study is the first to show that the PAVS-method is a feasible method for quickly (less than 1 minute) identifying patients with bipolar disorder who do not comply with these guidelines and therefore are at risk and in need for physical activity support and / or counseling as part of their routine treatment. This is of high clinical significance given growing calls for novel interventions aiming to reduce the burden of preventable cardiovascular diseases in this population. Of interest is as well that 46 of 65 participants or 71% adhered to the physical activity recommendations. A possible reason for this high rate might be that physical activity is considered a cornerstone in the multidisciplinary in- and outpatient treatment of people with bipolar disorder in Belgium (Probst, 2012; Probst et al., 2010).

4.2. Practical implications

The current data show that, as physical inactivity is a leading global contributor to cardiovascular diseases and premature mortality (Biswas et al., 2015; Wilmot et al., 2012), the PAVS may be an important vital sign in people with bipolar disorder. The brevity of the PAVS, along with the implementation of multidisciplinary care, may help promote the importance of physical activity assessment and prescription as a core part of the treatment of people with bipolar disorder. Whilst physical therapists and exercise physiologists have a key role in leading the design and delivery of

physical activity interventions, each member of the multidisciplinary team can play an important role in encouraging patients to engage in routine physical activity. For example, in addition to assessing the usual vital signs, nurses and other members of the multi-disciplinary team could utilize the PAVS-questions while recording the answers in an individual's baseline assessment (Happell et al., 2014). During the subsequent consultation, the psychiatrist could provide positive reinforcement to patients achieving 150 min of physical activity while advising them to maintain their physical activity behavior. Those patients who are not managing to achieve 150 minutes per week should be advised to become more active and informed about local opportunities such as exercise groups. If time permits, the psychiatrist could briefly explore the patient's readiness for change as it relates to their physical activity (Vancampfort et al., 2014), and use evidence-based behavior change principles to guide patients toward a more physically active lifestyle (Vancampfort et al., 2013b). When time does not permit, or when patients are confronted with severe depressive or manic symptoms and are consequently struggling to be more physically active (Vancampfort et al., 2013a) and/or those who are suffering from cardiovascular, respiratory, neurological or musculoskeletal conditions, may also benefit from further evaluation by a physical therapist or exercise physiologist (Stubbs et al., 2014). A longitudinal observational cohort systematically collecting PAVS-information during outpatient visits in the general population demonstrated that significant changes in physical activity behavior and health outcomes (e.g. greater relative weight loss and in patients with diabetes greater relative HbA1c decline) were observed concluding that the PAVS-method represents a valuable first step towards addressing the problem of inadequate physical activity (Grant et al., 2014). A longitudinal study of this nature is currently lacking in people with bipolar disorder, but would be valuable to see if such changes are replicated in this at risk group.

4.3. Limitations

Whilst the current findings are novel and promising, they should be interpreted in light of some limitations. First, although our data offer some preliminary evidence for the "concurrent validity" of the PAVS-method to identify cardio-metabolic risk and impaired functional exercise capacity, the "construct validity" and test-retest reliability of this self-report instrument in this population are unknown. Future research should therefore test its reliability and compare the minutes of physical

activity reported with the PAVS-method with an objective criterion (accelerometers). Secondly, cross-sectional nature of our study precludes any definitive conclusions to be made regarding the directionality of the relationships we observed. Future research should investigate the clinical impact of an intervention program designed to systematically ascertain patient-reported physical activity levels at the beginning of each outpatient visit. Thirdly, we did not include parameters such as socio-economic status, educational level, level of manic symptoms, bipolar subtype, other lifestyle factors such as smoking or unhealthy diet, and the presence of psychiatric and somatic co-morbidities in order to increase the external validity. Fourthly, whilst we observed no significant interactions with demographic variables (age and gender) in our preliminary analysis, future research is required to build upon our study and establish if the relationships observed are evident after adjusting for other potentially important confounders. Fifth, we did not include a power analysis nor did we correct for multiple testing. Finally, the internal validity of the current data is compromised by the lack of a healthy control group.

5. Conclusion

Our current data show that patients with bipolar disorder who do not meet the recommended physical activity recommendations of 150 minutes per week, as assessed by the quick PAVS-method have a higher risk for cardio-metabolic diseases and an impaired functional exercise capacity than patients complying with these recommendations. The current data offer preliminary evidence that the PAV-S might be an important vital sign in people with bipolar disorder. The brevity of the PAVS may help promote the importance of physical activity assessment and prescription as a core part of the treatment of people with bipolar disorder.

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Figure 1. Flowchart of the eligible in- and outpatients with bipolar disorder

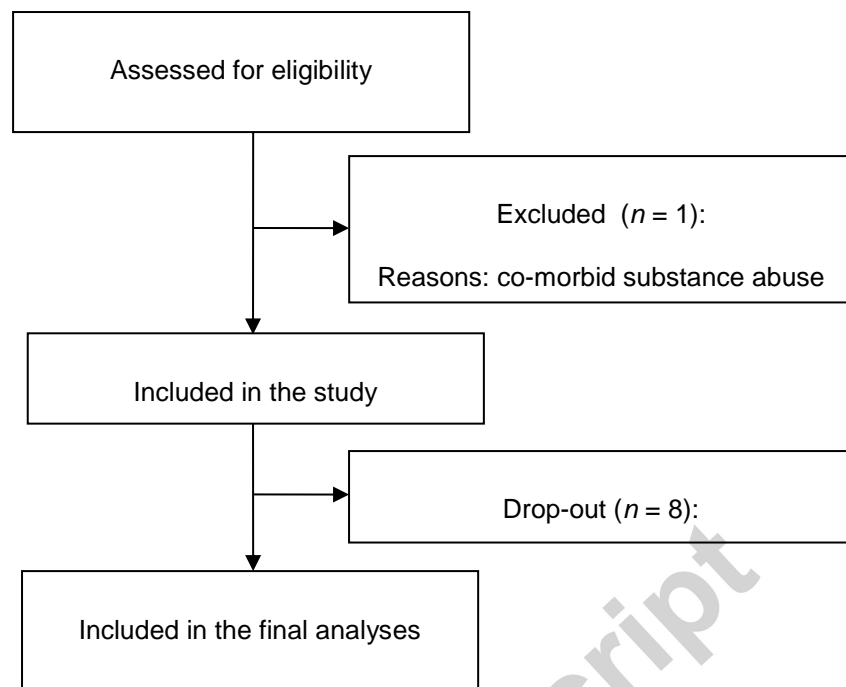


Table 1. Cardio-metabolic characteristics of people with bipolar disorders adhering versus not adhering to the physical activity recommendations

Variables	Not adhering (n=19)	Adhering (n=46)	P age	P gender	F compliance	P adherence
Body mass index (kg/m ²)	28.8±5.2	25.1±3.4	0.67	0.22	12.4	0.001*
6MWT score (m)	521.5±134.2	654.5±86.7	0.019	0.003	17.7	<0.001*
Abdominal obesity: n (%)°			0.48	0.89	6.4	0.014*
Yes	16 (24.6%)	24 (36.9%)				
No	3 (4.6%)	22 (33.9%)				
Hypertension: n (%)°			0.31	0.23	4.4	0.041*
Yes	10 (15.4%)	11 (16.9%)				
No	9 (13.8%)	35 (53.9%)				
Dyslipidemia: n (%)°			0.73	0.83	1.2	0.28
Yes	11 (16.9%)	20 (30.8%)				
No	8 (12.3%)	26 (40.0%)				
Hyperglycemia: n (%)°			0.29	0.20	16.3	<0.001*
Yes	11(16.9%)	4 (6.1%)				
No	8 (12.3%)	41 (63.1%)				
Metabolic syndrome: n (%)°			0.39	0.23	16.1	<0.001*
Yes	14 (21.5%)	10 (15.4%)				
No	5 (7.7%)	36 (55.4%)				

Minimal health recommendation=150min per week of moderate to vigorous physical activity, overweight when $BMI \geq 25$, °following the International Diabetes Federation criteria (Alberti et al., 2005), *ANCOVA controlling for age and gender significant when $P < 0.05$.

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Table 2. Unadjusted relative risk (RR) and 95% confidence interval (95%CI) for not adhering vs. adhering to the minimum physical activity recommendation

Variable	RR (95%CI)
Abdominal obesity (yes vs. no)	1.61 (1.15-2.26)
Hypertension (yes vs. no)	2.22 (1.13-4.30)
Dyslipidemia (yes vs. no)	1.33 (0.80-2.21)
Hyperglycemia (yes vs. no)	5.33 (2.14-13.27)
Metabolic syndrome (yes vs. no)	3.39 (1.84-6.24)

Highlights

- Physical activity should be assessed as a vital sign during every consult.
- Those who don't adhere to the health recommendations are less physically fit.
- Those who don't adhere to the health recommendations are at a higher metabolic risk.
- The brevity of the "vital sign method" may help promote physical activity prescription.